REMARKS

Amendments to the Claims

Claims 4-5, 11-13, 17 and 20 have been canceled.

Claims 1, 3, 7 and 8 have been amended.

New Claims 21-31 have been added.

Claims 1, 3 and 7-8 have been amended to recite TNFα-mediated "disease which results in joint stiffness," and to delete reference to ankylosis. Support for these amendments can be found in the specification, for example, at page 13, lines 1-8; page 13, line 26; page 57, lines 25-27; page 57, lines 25-27; page 58, line 1 to page 59, line 14; page 64, lines 3-26; page 100, line 25 to page 101, line 24; page 101, Table 5; page 104, Table 7 and Table 8; and page 105, line 8 to page 106, line 3. In addition, support is found in priority application 07/943,852, filed September 11, 1992, for example, at page 13, lines 5-10; page 13, lines 24-29; page 40, line 35 through page 41, line 6; page 45, lines 25-27; page 46, lines 6-17; page 47, lines 11-32; page 89, lines 12-27; page 90, Table 6; page 91, Table 7; page 91, line 27 to page 92, line 1; and page 92, line 20 to page 93, line 2.

Claims 1 and 3 have been amended to recite that the antibody or antigen-binding fragment competitively inhibits binding of A2 to human TNFα. Reference to cA2 has been deleted. Support is found in the specification, for example, at page 19, line 17 to page 20, line 2 and page 30, lines 5-12. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 12, line 24 to page 13, line 4; page 14, lines 3-9; and page 19, lines 3-10.

Claims 1 and 3 have been further amended to recite "ATCC Accession No. PTA-7045" Support for these amendments is found in the specification, as amended, for example, at page 25, lines 16-23. In addition, support for reference to the cell line for the A2 antibody is found in the priority application US Serial No. 07/670,827, filed March 18, 1991, at page 19, lines 14-20.

Claims 1 and 3 have been amended to recite "antigen-binding fragment." Support is found in the specification, for example, at page 9, lines 8-11 and page 17, lines 2-8. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 1, lines 5-12 and page 11, lines 10-20.

Claim 1 has been further amended to recite "human constant region." Claim 3 has been amended to recite "human IgG1" constant region. Support is found in the specification, for example, at page 10, lines 8-15; page 31, line 6 to page 32, line 2; and page 34, lines 16-21. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 9, lines 21-23; page 12, lines 18-26; page 26, lines 6-19; and page 52, lines 18-20.

Claims 1 and 3 have been further amended to recite that the antibody or antigen-binding fragment "binds to a neutralizing epitope of human TNFα *in vivo* with an affinity of at least 1 x 10^8 liter/mole, measured as an association constant (Ka), as determined by Scatchard analysis." Support is found in the specification, for example, at page 21, lines 16-23; page 60, line 25 to page 61, line 5; and Example X, particularly at page 80, line 24 to page 81, line 12. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 13, lines 5-8; page 18, lines 17-19; page 20, lines 3-6; and Example X, particularly, at page 67, line 12 to page 68, line 25.

New Claim 21 is directed to the method of Claim 1, wherein said antigen-binding fragment is selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv. Support is found in the specification, for example, at page 26, line 4. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 20, lines 16-19.

New Claim 22 is directed to the method of Claim 1, wherein said antibody or antigen binding fragment is of immunoglobulin class IgA, IgG1, IgG2, IgG3, IgG4 or IgM. Support is found in the specification, for example, at page 17, lines 19-21; page 31, lines 6-13; and page 125, lines 14-17. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 26, lines 6-19.

New Claim 23 is directed to the method of Claim 1, wherein said antibody or antigen-binding fragment comprises a human constant region and a human variable region. Support is found in the specification, for example, at page 9, lines 8-11; and page 31, line 3 to page 32, line 2. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 12, lines 8-25.

New Claim 24 is directed to the method of Claim 1, wherein said antibody or antigen-binding fragment comprises at least one human light chain and at least one human heavy chain. Support is found in the specification, for example, at page 19, lines 1-6; and page 31, line 3 to page 32, line 2. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 12, lines 8-25.

New Claim 25 is directed to the method of Claim 1, further comprising administering to the human an effective amount of an anti-inflammatory agent effective to treat the TNFα mediated disease which results in joint stiffness. New Claim 26 is directed to the method of Claim 25, wherein the anti-inflammatory agent is selected from the group consisting of: pentasa, mesalazine, asacol, benorylate, fenbufen, etodolac, indomethacin and aspirin. New Claim 27 is directed to the method of Claim 1, further comprising administering to the human an effective amount of a pain control agent to treat pain associated with the TNFα-mediated disease which results in joint stiffness. New Claim 28 is directed to the method of Claim 27, wherein the pain control agent is selected from the group consisting of: paracetamol and dextropropoxyphene. New Claim 30 is directed to the method of Claim 25, wherein the anti-inflammatory agent is selected from the group consisting of: codeine phosphate, naprosyn, diclofenac and ibuprofen. Support is found in the specification, for example, at page 102, Table 5; page 103, Table 6; pages 112-113, Table 11; and page 115, Table 12. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 43, lines 1-18. Further, support is found in the specification of priority application US Serial No. 07/943,852, filed September 11, 1992, for example, at page 90, Table 4 and Table 5.

New Claim 29 is directed to the method of Claim 1, further comprising administering to the human an effective amount of a disease-modifying anti-rheumatic drug. Support is found in the specification, for example, at Example XXIV, particularly at page 131, lines 3-8 and page 134, lines 11-13; and page 136, Table 15. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 43, lines 1-18. Further, support is found in the specification of priority application US Serial No. 07/943,852, filed September 11, 1992, for example, at page 90, Table 4 and Table 5.

New Claim 31 is directed to the method of Claim 1, further comprising administering to the human an effective amount of methotrexate. Support is found in the specification, for

example, at page 62, line 24 to page 63, line 2. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 43, lines 1-18. Further, support is found in the specification of priority application US Serial No. 07/943,852, filed September 11, 1992, for example, at page 90, Table 4 and Table 5.

No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Amendments to the Specification

Applicants have amended the specification to correct the spelling of "Geysen" on page 86, line 26 to page 87, line 12. Applicants submit evidence that the correct spelling is "Geysen" in the enclosed Abstract (Exhibit A).

Further, Applicants have amended the specification at page 25, lines 16-23 to recite "ATCC Accession No. PTA-7045," and to recite that c134A was deposited pursuant to the Budapest Treaty requirements with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 22, 2005. Support for this Amendment is found in the specification, for example, at page 25, lines 16-23. In addition, support for reference to the cell line for the A2 antibody is found in the priority application US Serial No. 07/670,827, filed March 18, 1991, at page 19, lines 14-20.

No new matter has been added by these amendments. Therefore, entry of these amendments into the application is respectfully requested.

Priority

The Examiner states that neither the priority applications nor the instant application provides a sufficient description of a representative number of species to represent the entire genus of "ankylosis" or "TNF-α-mediated ankylosis", as currently claimed.

While Applicants respectfully disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, Claims 4-5, 11-13, 17 and 20 have been canceled. Claims 1, 3 and 7-8 have been amended to recite "TNFα-mediated disease which results in joint stiffness." Support for these amendments can be found in priority application 07/943,852, filed September

11, 1992, for example, at page 13, lines 5-10; page 13, lines 24-29; page 40, line 30 through page 41, line 6; page 45, lines 25-27; page 46, lines 6-17; page 47, lines 11-32; page 89, lines 12-27; page 90-91, Table 6; page 91, Table 7; page 91, line 27 to page 92, line 1; and page 92, line 20 to page 93, line 2.

Therefore, the priority application 07/943,852 (filed September 11, 1992) provides sufficient written description for Applicants' claimed methods of treating TNFα-mediated disease which results in joint stiffness, and Applicants are entitled to claim the benefit of it. This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120. Therefore, the priority of all pending claims is at least September 11, 1992.

Objection Under 35 U.S.C. § 132

The Amendment filed on April 8, 2005 is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. The Examiner states that "[t]he added material which is not supported by the original disclosure is as follows: 'joint ankylosis' or 'TNF-α-mediated joint ankylosis' in terms of the claimed methods.'"

While Applicants respectfully disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, Applicants have canceled the reference to ankylosis on page 58, line 1 through page 59, line 14. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5 and 7-20 Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5 and 7-20 have been rejected under 35 U.S.C. 112, first paragraph as lacking written description. The Examiner states that "[t]he specification as originally filed does not provide support for the invention as now claimed: 'joint ankylosis' or 'TNF-α-mediated joint ankylosis.'"

While Applicants respectfully disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, Claims 4-5, 11-13, 17 and 20 have been canceled. Claims 1, 3, 7 and 8 have been amended to recite "TNFα-mediated disease which results in joint stiffness", thereby rendering

the rejection moot. Support for these claim amendments is found in the specification, for example at page 13, lines 1-8; page 13, line 26; page 57, lines 25-27; page 57, lines 25-27; page 58, line 1 to page 59, line 14; page 64, lines 3-26; page 100, line 25 to page 101, line 24; page 101, Table 5; page 104, Table 7 and Table 8; and page 105, line 8 to page 106, line 3.

Therefore, the application provides sufficient written description for Applicants' claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5 and 7-20 Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5 and 7-20 have been rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that the cA2 antibody must be known and readily available to the public, or obtainable by a repeatable method set for in the specification, or else a deposit of the cell line/hybridoma may be made in order to satisfy the enablement requirement.

37 C.F.R. § 1.809 (b)(1) states that "[t]he applicant for patent or patent owner shall reply to the rejection under paragraph (a) of this section by (1) In the case of an applicant for patent, either making an acceptable original...deposit, or assuring the Office in writing that an acceptable deposit will be made...." In addition, 37 C.F.R. § 1.809 (d) states that "[f]or each deposit made pursuant to these regulations, the specification shall contain: (1) The accession number for the deposit; (2) The date of deposit; (3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and (4) The name and address of the depository."

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to expedite prosecution, and in accordance with 37 C.F.R. § 1.809 (b)(1), on September 22, 2005, Applicants deposited the cell line for the A2 antibody (designation c134A) with American Type Culture collection (ATCC) under the Budapest Treaty. The ATCC accession number is PTA-7045.

The specification at page 25, lines 16-23 has been amended to recite "As examples of antibodies according to the present invention, murine mAb A2 (ATCC Accession No. PTA-

7045) of the present invention is produced by a cell line designated c134A." The specification at page 25, lines 16-23 has been further amended to recite "c134A was deposited pursuant to the Budapest Treaty requirements with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 22, 2005."

Further, Claims 1 and 3 have been amended to delete reference to cA2 and to recite "ATCC Accession No. PTA-7045" for the cell line of the A2 antibody. Dependent Claims 14-16 and 18-19 depend from these claims and, therefore, contain the same limitation. Claim 20 has been cancelled. Applicants reserve their rights to file continuing or divisional applications to pursue these claims.

Support for the amendments and the deposit of the cell line for the A2 antibody is found in the specification, for example, at page 25, lines 16-23. In addition, support is found in the priority application US Serial No. 07/943,852, filed September 11, 1992, at page 16, lines 25-35 and priority application US Serial No. 07/670,827, filed March 18, 1991, at page 19, lines 14-20.

Filed concurrently herewith is a Statement Under 37 C.F.R. §1.804, §1.806 and §1.808.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5 and 7-20 Under 35 U.S.C. § 112, second paragraph

A. Rejection of Claims 1, 3-5 and 7-20 under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected Claims 1, 3-5 and 7-20 under 35 U.S.C. § 112, second paragraph as being indefinite in the recitation of "cA2." Specifically, the Examiner states that "the use of 'cA2' antibody as the sole means of identifying the claimed antibody renders the claim indefinite because 'cA2' is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation [ ] to define completely distinct hybridomas / cell lines."

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, Claims 1 and 3 have been amended to delete reference to cA2 and to recite "ATCC Accession No. PTA-7045" for the cell line of the A2 antibody. As discussed above, on September 22, 2005, Applicants deposited the cell line for the A2 antibody with ATCC under the Budapest Treaty. The specification at page 25, lines 16-23 have been amended to recite the

ATCC accession number, the date of deposit, a description of the biological material and the name and address of the depository.

Reconsideration and withdrawal of the rejection are respectfully requested.

B. Rejection of Claims 1, 3-5 and 7-20 under 35 U.S.C. § 112, second paragraph.

The Examiner states that "the metes and bounds of said 'TNFα-mediated joint ankylosis' is ill-defined and ambiguous."

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, as discussed above, the paragraph at page 58, line 1 through page 59, line 14 has been amended to delete reference to "ankylosis." In addition, Claims 4-5, 11-13, 17 and 20 have been canceled. Claims 1, 3 and 7-8, as amended, no longer recite "TNFα-mediated joint ankylosis," and Claims 10, 14-16 and 18-19 depend from these claims, thereby rendering the rejection moot.

Reconsideration and withdrawal of the rejection are respectfully requested.

C. Claim 12 has been rejected under 35 U.S.C. § 112, second paragraph.

Claim 12 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "neutralizing epitope of human TNFα."

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, Claim 12 has been canceled, thereby rendering the rejection moot. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5 and 7-20 Under 35 U.S.C. § 102(b)

Claims 1, 3-5 and 7-20 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Le *et al.* (U.S. Patent No. 5,698,195). The Examiner states that:

> Le *et al.* teach methods of treating TNF-related pathologies, including rheumatoid arthritis (see column 34, line 53 and Claims) with TNF-α-specific antibodies, including recombinant and chimeric antibodies and the cA2 antibody specificity

> of the instant invention.... Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to treat rheumatoid arthritis with recombinant cA2-specific antibodies. A species anticipates a claim to a genus. See MPEP 2131.02.

Applicants' own priority patent Le *et al.* (5,698,195) is not prior art under 35 U.S.C. § 102 (b) because it was not published more than one year before Applicants' priority date. As indicated above, while Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, Applicants are entitled to priority to U.S. Application Serial No. 07/943,852 (filed September 11, 1992). The claims have been amended to recite deposit information and TNFα-mediated disease which results in joint stiffness. Le *et al.* (5,698,195) was filed over two years later, on October 18, 1994, and published on December 16, 1997.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-5 and 7-20 Under 35 U.S.C. § 103(a)

Claims 1, 3-5 and 7-20 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Le *et al.* (U.S. Patent No. 5,698,195) in view of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition.

The Examiner states that:

> Given the teachings of Le et al. to treat rheumatoid arthritis as well as targeting TNF in various tissues including joints (see column 34, paragraphs 3-4), one of ordinary skill in the art at the time the invention was made would have been motivated to target various conditions associated with joint ankylosis as taught by the Merck Manual, since the ordinary artisan would have an expectation of success in inhibiting the deleterious inflammatory responses associated with limiting joint movement common to various conditions associated with joint ankylosis.

To establish a prima facie case of obviousness, where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)) "Both the suggestion and the reasonable

expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* There must also be motivation or suggestion in the prior art to combine elements in the prior art. That is, in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. (*In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989))

As discussed above, Applicants' priority application, Le *et al.* U.S. Patent No. 5,698,195, is not prior art under 35 U.S.C. § 102 (b). It is also not prior art under 35 U.S.C. § 102 (a) or § 102 (e) because the publication is not "by another." The inventors listed in Le *et al.* U.S. Patent No. 5,698,195 are identical to the inventors of the subject application. In addition, the other cited reference, The Merck Manual of Diagnosis and Therapy, does not teach or suggest treatment of the recited pathology with Applicants' recited A2-specific anti-TNF antibodies. Thus, Applicants' claimed methods are not *prima facie* obvious, because one cited reference is not prior art and the other reference provides neither the requisite suggestion nor a reasonable expectation of success to arrive at the claimed invention.

Therefore, the rejection is moot. Reconsideration and withdrawal of the objection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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